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Sabiha Qazi
AU 1616
Mail BOx 2D19
Office 3B07

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Dehydroepiandrosterone Reduces Serum Low Density Lipoprotein Levels and Body Fat but Does not Alter Insulin Sensitivity in Normal Men*

JOHN E. NESTLER†, CORNELIUS O. BARLASCINI, JOHN N. CLORE, AND WILLIAM G. BLACKARD

Division of Endocrinology and Metabolism, Medical College of Virginia/Virginia Commonwealth University, Richmond, Virginia 23298

ABSTRACT. To assess the effects of dehydroepiandrosterone (DHEA) on body fat mass, serum lipid levels, and tissue sensitivity to insulin, five normal men were given placebo and five normal men were given oral DHEA [1600 mg/day (554.7 mmol/day)] for 28 days in a randomized, double blind study. In the DHEA group serum DHEA-S levels rose 2.5- to 3.5-fold, and mean (±SEM) serum androstenedione rose from 4.3 ± 0.6 to 8.6 ± 1.2 nmol/L ($P < 0.004$, by paired t test), but serum total testosterone, free testosterone, sex hormone-binding globulin, estradiol, and estrone levels did not change.

In the DHEA group the mean percent body fat decreased by 31%, with no change in weight. This suggests that the reduction in fat mass was coupled with an increase in muscle mass. DHEA administration also resulted in a fall in mean serum total cholesterol concentration (4.82 ± 0.21 *vs.* 4.48 ± 0.29 nmol/L; $P < 0.05$), which was due almost entirely to a fall of 7.5% in mean serum low density lipoprotein cholesterol (3.21 ± 0.11 *vs.* 2.97 ± 0.14 nmol/L; $P < 0.01$). No changes in anthropometric parameters or serum lipid levels occurred in the placebo group. Tissue sensitivity to insulin, assessed by the hyperinsulinemic-euglycemic clamp technique, did not change in either the placebo or DHEA groups.

These results suggest that in normal men DHEA administration reduces body fat, increases muscle mass, and reduces serum low density lipoprotein cholesterol levels. Tissue sensitivity to insulin was unaffected by short term DHEA administration. (*J Clin Endocrinol Metab* **66**: 57, 1988)

DEHYDROEPIANDROSTERONE (DHEA) is the most abundantly produced adrenal steroid, and serum concentrations of its sulfate ester, DHEA sulfate (DHEA-S), are approximately 20-fold higher than those of any other circulating steroid hormone. Peak serum DHEA and DHEA-S levels occur at age 25 yr, and they decrease rapidly thereafter, diminishing 95% by age 85–90 yr. All tissues studied to date contain steroid sulfatases which readily convert DHEA-S to DHEA, and DHEA has a high turnover rate. Despite the abundance and rapid turnover of the hormone, the physiological role of DHEA is unknown.

Recent interest in this hormone derives from its beneficial effects on obesity (1), lipids (2), and diabetes (3, 4) in animals. A study in man has demonstrated a striking inverse correlation between fetal serum DHEA-S and low density lipoprotein (LDL) levels (5), while a more recent study demonstrated an inverse correlation between serum DHEA-S levels and death from cardiovascular disease in adult men (6). There are, however, no *in vivo* studies on the effect of DHEA administration on body composition, serum lipid levels, or tissue sensitivity to insulin in normal man. We previously found that hyperinsulinemia reduced DHEA-S levels (7). In view of the report that DHEA increases tissue sensitivity to insulin in normal mice (4), we speculated that in response to insulinopenia the body might raise serum DHEA-S levels in order to increase its sensitivity to insulin, whereas during hyperinsulinemia serum DHEA-S would be reduced (7). In this manner DHEA-S would act as an endogenous regulator of tissue sensitivity to insulin. These observations also suggest that DHEA-S might exert some of its effects on carbohydrate tolerance, obesity, and lipids by altering insulin sensitivity.

To test the hypotheses that DHEA administration would decrease body fat content, decrease serum cholesterol levels, and increase tissue sensitivity to insulin, we conducted a prospective, randomized, double blind study in which normal men received either DHEA [1600 mg/day (554.7 mmol/day)] or placebo for 28 days. Before and after DHEA or placebo administration, anthropometric parameters, serum lipid levels, and tissue sensitivity to insulin were determined.

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Address all correspondence and requests for reprints to: John E. Nestler, M.D., Division of Endocrinology and Metabolism, Medical College of Virginia, MCV Station, Box 111, Richmond, Virginia 23298.

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† Recipient of a Clinical Associate Physician award from the NIH.

Materials and Methods

Protocol

Ten normal men were divided into two age-matched [placebo group: 24.5 ± 1.1 (±SD) yr; range, 22.4–25.2 yr; DHEA group: 23.7 ± 0.9 yr; range, 22.4–25.0 yr] and weight-matched groups (Table 1), each consisting of five subjects. The range of body mass index (BMI) values was similar in both groups (placebo group, 20.5–29.3 kg/m^2; DHEA group, 20.0–30.0 kg/m^2). None of the men was taking any medications, and none had a family history of diabetes mellitus. The study was approved by the Committee on the Conduct of Human Research of the Medical College of Virginia, and informed consent was obtained from each man.

On day 0 of the study, the men were admitted to the Clinical Research Center of the Medical College of Virginia at 0800 h after an overnight fast, and blood samples were obtained for determination of serum steroid, sex hormone-binding globulin (SHBG), lipid, glucose, and insulin concentrations. Tissue sensitivity to insulin then was assessed using the hyperinsulinemic-euglycemic clamp technique. Catheters were inserted into the right antecubital vein for infusion of insulin and glucose and into the left antecubital vein for blood withdrawal. Human regular insulin (Novolin, Squibb-Novo, Princeton, NJ) was infused via a Harvard pump (Harvard Apparatus, Millis, MA) at a rate of 4.0 mU/kg·min (29 pmol/kg·min) for 2 min, followed by 2.0 mU/kg·min (14 pmol/kg·min) for 6 min, and then at 1.0 mU/kg· min (7 pmol/kg·min) for the remainder of the study. Serum glucose was kept constant at the fasting level by bedside serum glucose determinations every 5 min and appropriate adjustment of a variable infusion of 25% glucose. The clamp was maintained for 120 min, and the average glucose infusion rate required to maintain euglycemia during the last 30 min of the clamp was used as the index of tissue sensitivity to insulin (M). It was assumed that endogenous glucose production was negligible during this time period (8). The mean coefficient of variation for the clamp studies performed on day 0 was 6.4% (n = 10).

The men then took orally, in a double blind fashion, capsules containing either placebo or 400 mg (138.7 mmol) DHEA four times daily [total daily DHEA dose, 1600 mg (554.7 mmol)] for 28 days. They were not instructed to change their dietary habits or lifestyle in any way. Although activity level and diet were not monitored, at the conclusion of the study each man denied any change in these parameters. No side-effects were noted in either group. The men returned on days 7, 14, and 21 for repeat measurements of serum DHEA-S levels. On day 28, the day 0 studies, including the clamp study, were repeated. The mean coefficient of variation for the clamp studies performed on day 28 was 6.0% (n = 10).

TABLE 1. Anthropometric data in the study subjects before and after placebo or DHEA administration

	Placebo group (n = 5)		DHEA group (n = 5)	
	Day 0	Day 28	Day 0	Day 28
Wt (kg)	75.7 ± 7.0	74.3 ± 7.0	77.5 ± 3.4	78.2 ± 3.5
BMI (kg/m^2)	24.6 ± 1.6	24.7 ± 1.5	23.9 ± 1.7	24.1 ± 1.7
% Body fat (%)	16.9 ± 3.5	16.7 ± 2.2	15.9 ± 3.7	10.9 ± 1.2

Values are expressed as the mean ± SEM. The measurements were performed, as described in the text, before and after the administration of either placebo or DHEA [1600 mg/day (554.7 mmol/day)] for 28 days.

Anthropometric measurements

Anthropometric parameters were measured within 1 week before day 0 of the study and within 1 week after day 28. All measurements were made by the same investigators (J.E.N. and C.O.B.). The men were weighed in both air and water using techniques developed by Behnke *et al.* (9). The latter determinations were done at maximal exhalation, and a correction factor of 1.45 L was used to account for residual air. A 9.09-kg weight was attached to each man to negate any buoyancy. Using the general formula for specific gravity, densities were obtained. Percent body fat was determined using the formula developed by Siri (10): percent body fat = [(4.95/density) − 4.50] × 100.

Assays

Serum glucose concentrations were determined by the glucose oxidase method. Serum insulin levels were determined by RIA (11). Serum DHEA-S levels were determined using a commercial antibody-coated tube kit (Pantex, Santa Monica, CA).

Serum androstenedione (A), estrone (E_1), and 17β-estradiol (E_2) concentrations were measured by RIA, as previously described (12). Serum (1.0 mL) was extracted with diethyl ether, and steroids were isolated by Sephadex LH-20 column chromatography. Highly specific antisera were used to measure A, E_1, and E_2. ^{3}H-Labeled steroids were added to serum before extraction to account for procedural losses. The antisera to A and E_2 were kindly provided by Dr. John Resko, Department of Physiology, University of Oregon School of Medicine (Portland, OR). Antiserum to E_1 was purchased from Steranti Research Ltd. (London, England).

Serum total testosterone (T) concentrations were determined using a commercial RIA kit (Diagnostic Products, Los Angeles, CA) (13). SHBG was determined by [^{3}H]dihydrotestosterone saturation (13). Free T (*i.e.* non-SHBG-bound T) was calculated from the total molar concentrations of T and SHBG according to a modification of the mass equation of Pearlman (14): $(x/T - x)\,(1/SHBG) = k(1 - x/SHBG)$; $x = (b - \sqrt{b^2 - 4a})/2$, where x is the molar concentration of SHBG-bound T, k is the association constant of T and SHBG, a = testosterone × SHBG, and $b = 1/k$ + SHBG + testosterone.

Serum total cholesterol and triglyceride levels were measured using established enzymatic methods (Nichols Institute, San Juan Capistrano, CA) (15). After precipitation of other lipid components with sodium phosphotungstate, high density lipoprotein (HDL) cholesterol was measured enzymatically (15). Very low density lipoprotein (VLDL) cholesterol levels were calculated using the formula: VLDL cholesterol = triglycerides/5. LDL cholesterol levels were calculated using the formula: LDL cholesterol = total cholesterol − (HDL cholesterol + VLDL cholesterol).

All hormone, SHBG, and lipid measurements from an indi-

vidual man were determined in duplicate in a single assay. The intraassay coefficient of variation of all assays was less than 8%.

Statistical analysis

All results are reported as the mean ± SEM. When comparisons within a group were made, data were analyzed by Student's two-tailed paired t test. When comparisons between groups were made, Student's two-tailed unpaired t test was used. $P < 0.05$ was considered significant.

Results

Effect of DHEA administration on serum DHEA-S levels and body composition

Weekly mean serum DHEA-S levels did not change in the placebo group, but rose 2.5- to 3.5-fold in the DHEA group (Table 2). No change in any anthropometric measurement occurred in the placebo group (Table 1). In the DHEA group, however, percent body fat decreased in four of the five men, with a mean decrease of 31% (Table 1). The single man in the DHEA group who did not lose body fat was the leanest subject in that group (BMI = 20.0 kg/m^2) and weighed about 90% of ideal body weight. No weight change occurred in the DHEA group.

Effect of DHEA administration on serum lipid concentrations

Serum total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and triglyceride concentrations did not change in the placebo group (Table 3). In the DHEA group, however, the mean serum total cholesterol concentration fell 7.1% ($P < 0.05$), and the mean serum LDL cholesterol concentration fell 7.5% ($P < 0.01$; Table 3). Mean serum HDL cholesterol, VLDL cholesterol, and triglyceride concentrations did not change in the DHEA group.

It should be noted that the fall in serum LDL cholesterol in the DHEA group assumes that DHEA administration did not alter the composition (*i.e.* triglyceride to cholesterol mass ratio) of VLDL particles.

TABLE 2. Serum DHEA-S concentrations in the study subjects before and during placebo or DHEA administration

	DHEA-S (μmol/L)				
	Day 0	Day 7	Day 14	Day 21	Day 28
Placebo group (n = 5)	9.9 ± 1.5	10.7 ± 2.6	11.0 ± 2.2	10.4 ± 2.3	8.7 ± 1.7
DHEA group (n = 5)	10.9 ± 1.9	33.1 ± 7.6	39.7 ± 12.5	30.6 ± 9.3	38.8 ± 11.2

Values are expressed as the mean ± SEM.

TABLE 3. Serum total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and triglyceride concentrations before and after the administration of either placebo or DHEA [1600 mg/day (554.7 mmol/day)] for 28 days

	Placebo group (n = 5)		DHEA group (n = 5)	
	Day 0	Day 28	Day 0	Day 28
Cholesterol (mmol/L)	4.73 ± 0.34	4.66 ± 0.37	4.82 ± 0.21	4.48 ± 0.29*
HDL cholesterol (mmol/L)	1.24 ± 0.04	1.12 ± 0.05	1.09 ± 0.11	1.01 ± 0.09
LDL cholesterol (mmol/L)	3.04 ± 0.39	3.10 ± 0.34	3.21 ± 0.11	2.97 ± 0.14†
VLDL cholesterol (mmol/L)	0.45 ± 0.04	0.43 ± 0.05	0.53 ± 0.10	0.50 ± 0.11
Triglycerides (mmol/L)	0.98 ± 0.08	0.96 ± 0.11	1.14 ± 0.22	1.07 ± 0.23

Values are expressed as the mean ± SEM.
* $P < 0.05$ compared to day 0 value of DHEA group.
† $P < 0.01$ compared to day 0 value of DHEA group.

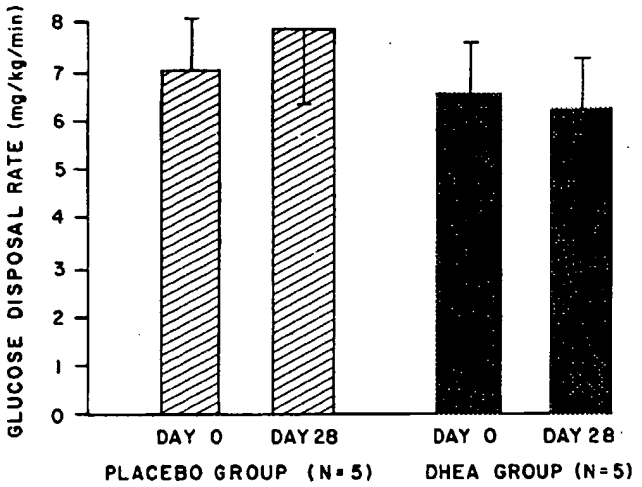

FIG. 1. Mean (±SEM) glucose disposal rates during the final 30 min of the hyperinsulinemic-euglycemic clamp studies. Five men took placebo and five men took DHEA [1600 mg/day (554.7 mmol/day)] for 28 days. Tissue sensitivity to insulin (M) was determined by the hyperinsulinemic-euglycemic clamp technique, as described in the text, both before (day 0) and after (day 28) drug administration. To convert glucose disposal rates to micromoles per kg/min, multiply by 5.51.

Effect of DHEA administration on tissue sensitivity to insulin

The day 0 and day 28 mean fasting serum glucose levels were similar in both the placebo group (5.0 ± 0.2 *vs.* 5.4 ± 0.1 mmol/L; P = NS) and the DHEA group (4.9 ± 0.1 *vs.* 5.1 ± 0.1 mmol/L; P = NS). Fasting serum insulin levels on day 0 and day 28 were also similar in both groups [placebo group, 118 ± 11 *vs.* 91 ± 13 pmol/L (P = NS); DHEA group, 105 ± 17 *vs.* 90 ± 8 pmol/L (P = NS)].

In the placebo group, tissue sensitivities to insulin (M) on day 0 and day 28 were similar (39.1 ± 5.5 *vs.* 43.5 ± 8.8 μmol glucose/kg·min; P = NS; Fig. 1), as measured by the hyperinsulinemic-euglycemic clamp technique. Likewise, tissue sensitivities to insulin were similar on day 0 and day 28 in the DHEA group (36.4 ± 5.0 *vs.* 34.7

± 5.5 μmol glucose/kg·min; P = NS; Fig. 1). The day 0 and day 28 steady state insulin levels (during the 30- to 120-min period of the clamp) in the placebo group (494 ± 39 *vs.* 433 ± 23 pmol/L; P = NS) and DHEA group (462 ± 65 *vs.* 504 ± 60 pmol/L; P = NS) were comparable.

Effect of DHEA administration on serum A, E_1, E_2, total T, free T, and SHBG concentrations

Serum A concentrations were similar in the placebo and DHEA groups on day 0 (Table 4), and serum A did not change in the placebo group during the study. In the DHEA group, however, the mean serum A concentration increased 2-fold ($P < 0.004$; Table 4). Serum E_1, E_2, total T, free T, and SHBG concentrations did not change in either the placebo or DHEA group (Table 4).

Discussion

Despite characteristics which suggest that DHEA is a biologically active hormone, its physiological role is unknown. Claims have been made that DHEA may prevent obesity, aging, diabetes mellitus, and heart disease (16). These assertions stem from animal studies which demonstrated that DHEA administration resulted in lower body weight in C3H(Avy/a) mice without affecting appetite or food intake (1), prevented the development of diabetes in genetically diabetic (−db/db) (3, 4) or obese (−ob/ob) mice (4), increased tissue sensitivity to insulin in aged normal mice (4), and prevented the rise in cholesterol levels of rats made hypothyroid with propylthiouracil (2). Compatible with these findings are human studies demonstrating an inverse relationship between fetal serum LDL and DHEA-S levels (5) and between cardiovascular death and serum DHEA-S levels in adult men (6).

Our interest in DHEA was stimulated by our finding of an unexpected decline in serum DHEA-S levels in women during sustained supraphysiological hyperinsulinemia (7). This observation coupled with the demonstration that DHEA increases insulin sensitivity of aged normal mice (4) suggested to us that DHEA may be an endogenous regulator of tissue sensitivity to insulin. Therefore, the beneficial effects of DHEA on obesity, diabetes, and lipids might be due to its effect on insulin sensitivity. This study was designed to test that hypothesis in a prospective manner, using the hyperinsulinemic-euglycemic clamp technique as a measure of insulin sensitivity. In addition, because of the paucity of data regarding the physiological actions of DHEA, we examined the effects of DHEA treatment on body composition and serum lipid levels.

DHEA administration for 28 days resulted in a marked decrease in percent body fat in four of the five men, despite no change in weight. The reduction in fat mass by DHEA may in part depend upon preexisting adiposity, since the maximal reduction in body fat occurred in the most obese man, whereas the single man who did not lose body fat was the leanest. The decrease in percent body fat in the absence of weight change suggests an increase in muscle mass coupled with a reduction in fat mass. Such anthropometric changes might have been predicted from the effects of pharmacological doses of other androgens (17). It is believed that androgens produce skeletal muscle cell hyperplasia by direct interaction with the T receptor, whereas the reduction in fat mass is due to their aromatization to estrogens in adipose tissue (17). Although serum E_1 and E_2 levels did not rise in the DHEA group, it is likely that the significant rises in serum DHEA-S and A resulted in increased aromatization of these androgens at the tissue level.

We also found a significant decrease in serum total cholesterol levels, which was almost entirely due to reductions in serum LDL cholesterol in the DHEA group. This finding contrasts with animal studies, in which DHEA prevented the rise in serum cholesterol levels in rats made hypothyroid with propylthiouracil, but had no effect on serum cholesterol levels in normal rats (2). The magnitude of the reduction in serum cholesterol levels by DHEA in our study represents an estimated 14% reduction in risk for the development of cardiovascular disease. The DHEA-induced fall in serum LDL cholesterol coupled with the inverse correlation between fetal serum DHEA-S and LDL levels reported by Parker, Jr. and co-workers (5) suggest that a decrease in this risk factor could conceivably play a role in the reported decreased risk of cardiovascular death in men with higher DHEA-S levels (6).

DHEA administration did not affect serum HDL cholesterol levels. The reduction in serum LDL cholesterol levels and absence of effect on serum HDL cholesterol levels contrast markedly with the effects of other androgens on lipids. Androgens typically raise serum LDL cholesterol levels and reduce serum HDL cholesterol levels (17). These changes are believed to account at least

TABLE 4. Serum E_2, E_1, A, total T, free T, and SHBG concentrations before and after the administration of either placebo or DHEA [1600 mg/day (554.7 mmol/day)] for 28 days

	Placebo group (n = 5)		DHEA group (n = 5)	
	Day 0	Day 28	Day 0	Day 28
E_2 (pmol/L)	117 ± 18	91 ± 11	117 ± 26	103 ± 6
E_1 (pmol/L)	193 ± 37	228 ± 38	194 ± 21	232 ± 19
A (nmol/L)	5.5 ± 0.2	5.8 ± 0.4	4.3 ± 0.6	8.6 ± 1.2*
Total T (nmol/L)	29.0 ± 3.1	30.4 ± 2.9	26.6 ± 2.2	30.0 ± 4.2
Free T (nmol/L)	12.9 ± 2.9	11.6 ± 2.0	11.0 ± 1.3	16.9 ± 2.2
SHBG (nmol/L)	17.9 ± 1.7	20.8 ± 1.3	17.5 ± 3.7	13.9 ± 3.0

Values are expressed as the mean ± SE.

* $P < 0.004$ compared to day 0 value of DHEA group.

in part for the increased risk for atherosclerosis and cardiovascular disease in men treated with anabolic steroids. The fall in serum LDL cholesterol in the DHEA group is more analogous to an estrogen effect (17).

Although serum DHEA-S and A levels rose in the DHEA group, SHBG levels did not change. Androgens may reduce serum SHBG levels directly, although some investigators postulate that androgens may also reduce serum SHBG indirectly by causing insulin resistance, which results in elevated insulin levels. Insulin *per se* lowers SHBG levels as well (Plymate, S. R., L. A. Matej, R. E. Jones, and K. E. Friedl, unpublished data). Our results are consistent with this possibility, since insulin levels and SHBG levels did not change in the DHEA group.

DHEA administration had no effect on tissue sensitivity to insulin, unlike androgen therapy, which results in decreased tissue sensitivity to insulin. The hyperinsulinemic-euglycemic clamp studies were not performed at an insulin concentration that would have resulted in maximal glucose uptake. Therefore, insulin responsiveness was not assessed. However, a change in insulin responsiveness seems unlikely in the absence of a change in insulin sensitivity. It is possible that DHEA administration might alter insulin sensitivity if administered for a longer duration or to a group of individuals with preexisting insulin resistance (*e.g.* type II diabetic patients).

In summary, DHEA administration appears to 1) reduce body fat mass and increase muscle mass, 2) lower serum LDL cholesterol levels, and 3) have no effect on tissue sensitivity to insulin. It is possible that the progressive decline in DHEA and DHEA-S levels with aging may play a part in the increase in body fat and increased atherosclerosis associated with growing older.

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